REMARKS

Applicants respectfully acknowledge the consideration and withdrawal of the finality of the rejection of the Office Action dated September 7, 2007, as indicated by the Examiner in the Office Action dated January 2, 2008, at page 2. Applicants also respectfully acknowledge the withdrawal of the 35 USC 112, ¶1 enablement rejection in the Office Action dated January 2, 2008.

I. 35 USC 112, ¶1 Written Description

Claims 67-70, 72-75 and 77-90 stand rejected under 35 USC 112, first paragraph, because

> the claims encompass a genus of compounds defined only by their function wherein the relationship between the structural features of members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed.

[Office Action dated January 2, 2008, at page 3; emphasis in the original.] The Office Action concludes by stating: "[N]o structural or specific functional characteristics of such an inhibitor is provided, nor is there any indication that the artisan actually implemented the method of [sic] so as to identify any inhibitor." [Office Action, middle of page 4.]

Applicants respectfully traverse, first relying on their arguments presented in their response dated June 27, 2007, in response to the previous 35 USC 112, ¶1 written description rejection of Claims 67-72 and 76-84 [Response, at pages 14-23]. In that response, Applicants pointed out that the subject claims were original claims and that "rejection of an original claim for lack of written description should be rare." [MPEP

§ 2163 (II)(A); emphasis added.] Further, as pointed out in the response dated June 27, 2007, the Specification provides specific direction for one of skill in the art for the selection and/or design of heterocyclic and aromatic organic CA IX-specific inhibitors, and conventional art teaches how to identify compounds other than those specifically disclosed in the Specification likely to preferentially bind CA IX. As argued at pages 17-20 of the response dated June 27, 2007, Applicants further respectfully submit that the Eli Lilly case, cited by the Examiner as support for a finding of lack of written description, is not analogous to the instant situation.

In addition, Applicants respectfully argue that the case law supports that a **pioneering invention** is entitled to a broad range of equivalents. As the instant invention is the first to describe CA IX-preferential inhibitors, it is entitled the status of a pioneering invention, particularly in view of the **successful** use of **virtual screening** for novel subnanomolar inhibitors of human carbonic anhydrase II [hCA II], based on similarity to known hCA II inhibitors [Grüneberg et al., J Med Chem, 45(17): 3588-3602 (2002); copy of Abstract enclosed]. Therefore, contrary to the statement at page 3 of the Office Action that "one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed . . . ," one of skill in the art would have considerable such knowledge beforehand.

Applicants will discuss the above points in greater detail below, and review the extensive guidance in the Specification for the design of CA IX-specific inhibitors by modification of their physico-chemical properties.

Original Claims

As argued by Applicants at pages 14-15 of the response dated June 27, 2007, numerous cases hold that an "original claim," that is, one contained in the specification when it is filed, complies with the Section 112 written description requirement. [See, for example, In re Koller, 204 USPQ 702 (CCPA 1980); Union Oil Co. of California v. Atlantic Richfield Co., 54 USPQ2d 1227 (Fed. Cir. 2000).] For example, the Court of Customs and Patent Appeals (CCPA) in In re Smith, 481 F.2d 910, 178 USPQ 620 at 623 (CCPA 1973) stated: "Where the claim is an original claim,

the underlying concept of insuring disclosure as of the filing date is satisfied, and the description requirement has likewise been held to be satisfied."

> The Manual of Patent Examining Procedure in Section 2163(I)-(II) states:
>
> There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims").
>
> . . . .
>
> Consequently, rejection of an original claim for lack of written description should be rare.

[Emphasis added.]

The PTO's Written Description Guidelines [Fed. Reg., Vol. 66, No. 4 (Jan. 5, 2001)] similarly indicate that there is a "strong presumption that an adequate written description of the claimed in invention is present when the application is filed, consistent with In re Wertheim, supra.

> The Guidelines emphasize that the burden of proof is on the **examiner to establish that a description as filed is not adequate and require the examiner to introduce sufficient evidence or technical reasoning to shift the burden of going forward with contrary evidence to the applicant.**

[*Id.* at page 1100, col.3; emphasis added.] Applicants respectfully submit that the Examiner has not introduced sufficient evidence to shift the initial burden of proof to the Applicants, but if hypothetically that burden had been shifted, the Applicants would have overturned that burden as explained in the discussion below in view of the discussion below regarding **pioneering inventions, success of virtual screening based on known compounds, and the guidance in the Specification**.

Case Law for Pioneering Inventions

The CCPA in In re Goffe, 191 USPQ 429 at 431 (CCPA 1976) criticized the U.S. Patent and Trademark Office for attempting to limit the appellant to specific claims, lest a competitor seeking to avoid infringement could achieve this goal readily by merely following the disclosure in the patent when it issues. The CCPA further stated:

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work . . . would not serve the constitutional purpose of promoting progress in the useful arts.

Applicants respectfully submit that CA IX-specific inhibition is a pioneering invention, and as such, is entitled to a broad range of equivalents. [A basic patent on a pioneering invention is entitled to be interpreted broadly. Texas Instruments, Inc. v. United States ITC, 231 USPQ 833 (Fed. Cir. 1986).] As the CCPA stated in In re Hogan and Banks, 194 USPQ 527, 537 (CCPA 1977):

> As pioneers, . . . they would **deserve broad claims to the broad concept. What were once referred to as 'basic inventions' have led to incentives, not only to invention and its disclosure, but to its prompt, early disclosure**.
> . . .
>
> . . . To restrict appellants to the crystalline form disclosed . . . would be a poor way to stimulate invention, and particularly to encourage its early disclosure. To demand such restriction is merely to state a policy against broad protection for pioneer inventions, a policy both shortsighted and unsound from the standpoint of promoting progress in the useful arts, the constitutional purpose of the patent laws.

[Emphasis added.]

The purpose recited in the U.S. Constitution for granting patents is "to promote the progress of science and the useful arts by securing for limited times to . . . inventors the exclusive right to their respective . . . discoveries." Applicants respectfully submit that the goal of the Constitution quoted above would not be served by limiting Applicants to the precise organic aromatic and heterocyclic compounds found by them to specifically inhibit CA IX activity, **particularly** in view of accelerated **virtual**

screening methods now available in the art of drug design, based on structural similarity to known inhibitors of a target ligand.

Virtual Screening

Methods for optimizing drug design are known in the art, and have been recently streamlined by accessible online databases that perform **virtual screening** of compound databases submitted by a user. One such online database is **BindingDB** (http://www.bindingdb.org), a publicly accessible database. The website provides web-accessible tools for virtual screening of candidate ligands against a given target, based in part on measured binding affinities for biomolecules. **CA IX is included as a target** (Target **80**, http://www.bindingdb.org/bind/ByTargetNames.jsp) along with **200 known ligands, including compounds disclosed in the instant Specification**. According to the BindingDB website ["Virtual Screening" page], it

> provides virtual screening tools to help identify the compounds in your own compound catalog that are most likely to be active against a desired target. . . . These methods need to be trained with a set of compounds known to be active. Two of the methods . . . also require a set of compounds presumed to be inactive (decoys).

The "actives" can be up to 100 compounds from a BindingDB search, or from uploaded compounds. The compounds are ranked according to the maximum Tanimoto similarity of each compound to any of the "actives," based on JChem fingerprints.

As described by Liu et al. [Liu et al., Nucleic Acids Research, 00 (Database Issue): D1-D4 (2006); copy enclosed]:

> The BindingDB website supports a range of query types, including searches by chemical structure, substructure and similarity; protein sequence; ligand and protein names; affinity ranges and molecular weight. . . . The data in BindingDB are linked both to structural data in the PDB [Protein Data Bank] via PDB IDs and chemical and sequence searches, and to the literature in PubMed via PubMed IDs.

[Liu et al., Abstract.]

Moreover, virtual screening has been used successfully to identify novel inhibitors of enzymes, including inhibitors of human carbonic anhydrase II [hCA II], based on similarity to known hCA II inhibitors [Taylor et al., Br J Pharmacol, 153: S55-S67 (2008), page S59, Table 3, copy enclosed; Grüneberg et al., J Med Chem, 45(17): 3588-3602 (2002), Abstract]. As stated by Grüneberg et al.:

> Virtual screening of compound libraries is an alternative and complementary approach to high-throughput screening in the lead discovery process. A new strategy is described to search for possible leads of human carbonic anhydrase II, applying a protocol of several consecutive hierarchical filters involving a preselection based on functional group requirements and fast pharmacophore matching. . . . **After examination of the affinity predictions, 13 compounds were selected for experimental testing. Of these 13, three could be shown to be subnanomolar, one is nanomolar, while a further seven are micromolar inhibitors. . . . The novelty of the discovered leads is best supported by the fact that a search in the patent literature showed the newly discovered subnanomolar compounds to comprise scaffolds not yet covered by existing patents.**

[Grüneberg et al., 2002, Abstract; emphasis added. Applicants respectfully point out that the publication date of the Grüneberg article is August 15, 2002, before the earliest priority date of the instant application, November 26, 2002.] That result reported by Grüneberg is a remarkable success: eleven out of thirteen candidate compounds had micromolar affinity, **four out of thirteen** candidates had **nanomolar** affinity! Applicants respectfully submit that armed with such tools and the compounds identified in the instant Specification (with their inhibition constants), the skilled artisan would only need to perform routine experimentation to identify additional heterocyclic and aromatic compounds that preferentially inhibit CA IX.

Structure-Function Analysis for CA IX-Specific Inhibitors

As stated above, the Examiner indicates that "the claims encompass a genus of compounds defined only by their function wherein the relationship between the structural features of members of the genus and said function have not been defined. " Applicants respectfully disagree. Even without the use of virtual screening, the skilled

artisan is provided with extensive guidance in the instant Specification for the preferred structures of CA IX-preferential inhibitors. As stated in the Summary of the Invention:

> The inventors evaluated inhibition profiles of CA IX with a series of aromatic and heterocyclic compounds and found that some of them inhibit CA IX more efficiently than the other widely distributed isoforms CA I, II and IV. Several nanomolar CA IX inhibitors have been detected both among the aromatic and the heterocyclic compounds. This finding is very promising for the design of CA IX-specific inhibitors by modification of their physico-chemical properties such as charge, size and bioreductivity to conform the characteristic properties of CA IX.

[Specification at page 8, lines 24-30; emphasis added.]

Conventional art teaches the structural requirements for carbonic anhydrase inhibition in general (infra). The instant Specification teaches additional structural requirements for MN/CA IX-specific inhibition. The claimed methods are directed to the use of CA IX-specific aromatic and heterocyclic inhibitors that have been screened for potent and selective inhibition of CA IX, and/or for membrane impermeance. The Specification provides not only numerous working examples of heterocyclic and aromatic CA IX-specific inhibitors [from Compounds 1-91, with inhibition constants (K_I) against CA isozymes I, II, IV and IX shown in Tables 1-3 of the Specification], but also structure-function analysis of the effectiveness of those ninety-one compounds in relation to CA IX's membrane localization and unique active site, which teachings constitute sufficient guidance to the skilled artisan for the design or selection of individual heterocyclic and aromatic organic CA IX-specific inhibitors. Any additional experimentation necessary to perform the diagnostic, prognostic or therapeutic methods of the claims as amended would be routine experimentation, within ordinary skill within the art.

Applicants respectfully submit that the written description requirement of 35 USC 112, first paragraph does not require that Applicants provide evidence that they have constructed or prepared the invention in question. "Possession may be shown in a variety of ways including . . . by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." [MPEP § 2163 (I).] Applicants respectfully submit that Claims 67-70, 72-75 and 77-90

claim methods using the subject inhibitor compounds in terms sufficiently "clear and concise and fully supported by the description" as required by the written description requirement of 35 USC 112, first paragraph.

Guidance in the Specification

A. Carbonic Anhydrase Inhibition (in General)

Because of the physiological importance of the 15 or so carbonic anhydrase isozymes in humans, there is already extensive conventional art in the field of CA inhibitor drug design, particularly for sulfonamides. At least 25 clinically used drugs have been reported to possess significant CA inhibitory properties, in addition to many other derivatives belonging to the sulfonamide, sulfamate or sulfamide families. [For a recent review, see Scozzafava et al., Expert Opin. Ther. Pat., 16: 1627–1664 (2006).] At the priority date of the instant application, that conventional art provided one of skill in the art with general guidance for design and selection of CA inhibitors. For example:

> Teicher et al . . . reported that acetazolamide – the prototypical CA inhibitor (CAI) – functions as a modulator in anticancer therapies, in combination with different cytotoxic agents, . . . , to suppress tumor metastasis and to reduce the invasive capacity of several renal carcinoma cell lines. . . . Such studies demonstrate that CAIs may be used in the management of tumors that overexpress one or more CA isozymes. . . .
>
> All the six classical CAIs (acetazolamide, methazolamide, ethoxzolamide, dichlorophenamide, dorzolamide, and dichlorophenamide) used in clinical medicine or as diagnostic tools, show some tumor growth inhibitory properties. . . .

[Specification, at page 4, line 21 to page 5, line 7.]

> Detailed structure-function analysis taught that
>
> enhancement of CA inhibitory activity is correlated with increased positive charges on the heterocyclic/aromatic ring . . . , as well as with 'long' inhibitor molecules *per se* (i.e., molecules extending on the direction passing through the

> Zn(II) ion of the enzyme, the sulfonamide nitrogen atom and the long axis of the inhibitor). . . .

[Specification at page 43, lines 14-18]. That conventional art still applies to selection of CA IX inhibitors; one of skill in the art would first look to compounds that would be expected to inhibit CAs.

However, prior art also indicated that CA IX-**specific** inhibition might not be possible: Wingo et al. [Biochem. Biophys Res Comm., 288: 666-669 (2001)] reported in 2001 that they had prepared "a truncated, recombinant form of human CA IX of 255 residues consistent with full-length human CA II. . . . Human CA IX was very strongly inhibited by three classic sulfonamides and cyanate, with inhibition constants that are close to those for CA II." [Abstract.] Wingo concluded that, because of the conservative nature of the amino acid differences between the active sites of human CA IX and CA II, "it is not surprising that their catalytic activities are similar." [Wingo, at page 668, col. 2.] However, the inventors not only performed detailed structure-function analysis of CA IX inhibition by compounds known to inhibit other CAs, but also designed CA IX-specific compounds, beginning with base compounds with potent carbonic anhydrase activity, such as aminobenzolamide: "It appeared thus of interest to try to explore this result, designing positively-charged, long sulfonamide CAIs. Thus, we thought of attaching substituted-pyridinium moieties to an already potent and long-molecule CAI suitable for reaction with pyrilium salts, i.e., aminobenzolamide." [Specification, at page 43, lines 18-22.]

B. CA IX-Specific Inhibition

For the first time, the Specification analyzes the active site of CA IX in detail, and shows how significant chemical and biological differences between MN/CA IX and other physiologically important CA isozymes can be exploited in the design of CA IX-specific inhibitors: 1) MN/CA IX is an integral plasma membrane protein with an active site exposed on the extracellular side; 2) MN/CA IX has a unique amino acid sequence at the active site, which site is **larger** than those of other CA isozymes; and 3) MN/CA IX is expressed (and activated) preferentially in hypoxic areas of tumors with

poor prognosis [Specification at page 8, lines 15-23]. That unique combination of attributes guides the design of CA IX-specific inhibitors.

Chemical Attributes of CA IX Inhibitors

General: In general, "CA IX is a sulfonamide avid CA . . ." [Specification, at page 48, lines 2-3], and a CA IX-specific inhibitor would preferably exhibit 1) high "positive charges on the heterocyclic/aromatic ring . . ." [for CA inhibition in general; Specification, at page 43, lines 9-20], 2) comprise a long molecule extending in the direction of the zinc ion of the enzyme [Ib.], and 3) have a positive, salt-like character overall [for membrane impermeance; Specification, at page 53, lines 11-14 and page 62, lines 28-32].

Specific: The instant Specification teaches that, among Compounds 1-91, several demonstrate a high preference for CA IX over any of the three other CA isozymes tested, including the physiologically most important isozymes CA II and CA IV. For example, Compounds 1, 6, 23-25 all show good selectivity ratios of CA IX over any of CA I, CA II and CA IV [Table 1, Specification at pages 60-61]. The Specification further teaches several distinctive characteristics of the CA IX active site which direct the skilled artisan for the design of additional potent and selective CA IX inhibitors.

By analyzing the relative effectiveness of Compounds 1-91 against CA isozymes I, II, IV and IX, the Specification teaches a number of important differences between the active site cavity of MN/CA IX's catalytic domain and that of the other widely distributed relevant carbonic anhydrase isoenzymes [Specification, at page 47, line 27 to page 54, line 22]. Such differences between the active sites of MN/CA IX and the other widely distributed, relevant CA isozymes taught in the Specification by preferences for specific compounds, can be used by those of skill in the art to choose lead compounds to design other organic heterocyclic and aromatic compounds to test in the representative screening assays disclosed in the Specification, for the functionalities required by the claimed methods.

Bulky Side-groups: A particularly significant difference between MN/CA IX's active site and that of other relevant CA isozymes is that MN/CA IX's active site is

"larger than that of the other investigated isoenzymes . . ." [Specification, page 9, lines 1-4]; therefore, bulky side-groups extending into the active site of the enzyme favor CA IX enzymatic specificity. The larger size of MN/CA IX's active site explains potentially why more bulky compounds that strongly inhibit MN/CA IX were weak inhibitors of CA I, II and IV. For example, the larger active site cavity of MN/CA IX is explained at page 53, line 32 to page 54, line 8, in relation to CA II, wherein that important difference is attributed to the amino acid at position 131, which is Phe for CA II, and Val for CA IX.

> An important difference is constituted by the amino acid in position 131, which is Phe for hCA II and Val for hCA IX. Phe 131 is known to be very important for the binding of sulfonamide inhibitors to hCA II . . . : in many cases this bulky side chain limits the space available for the inhibitor aromatic moieties, or it may participate in stacking interactions with groups present in it. . . . Thus, the presence of a less bulky such residue in hCA IX (i.e., a valine) which is also unavailable for participation to stacking interactions has as a consequence the fact that the hCA IX active site is larger than that of hCA II.

Derivatives/Moieties Favoring CA IX: Several more highly detailed conclusions were drawn from the comparative activities of Compounds 1-91 and taught in the Specification at the least at page 47, line 28 to page 54, line 22. Among them, for example, is the conclusion that while CA isozymes I, II and IV favor heterocyclic over aromatic sulfonamides, CA IX apparently does not [Specification, page 48, lines 9-13]. Of the CAs tested, CA IX alone favors orthanilamide derivatives, 1,3-benzene-disulfonamide derivatives, homosulfanilamide and 4-aminoethyl-benzenesulfonamide [Specification, at page 48, lines 13-21].

Polar Moieties: A potentially important amino acid residue difference between MN/CA IX and the physiologically important CA II is that at position 132, which is Gly (nonpolar, aliphatic amino acid) in CA II, and Asp (polar, uncharged amino acid) in CA IX.

> A second potentially important residue is 132, which is Gly in hCA II and Asp in hCA IX. This residue is situated on the rim of the hydrophilic half of the entrance to the active site of

> hCA II (and presumably also of hCA IX) and it is critical for the interaction with inhibitors possessing elongated molecules, as recenly shown by us. . . . Strong hydrogen bonds involving the CONH moiety of Gly 132 were shown to stabilize the complex of this isozyme with a *p*-aminoethylbenzenesulfonamide derived inhibitor. . . . In the case of hCA IX, the presence of aspartic acid in this position at the entrance of the active site may signify that: (i) stronger interactions with polar moieties of the inhibitor bound within the active site should be possible, since the COOH moiety possesses more donor atoms; (ii) this residue may have flexible conformations, fine-tuning in this way the interaction with inhibitors.

[Specification, at page 54, lines 8-19.]

Pyridinium Derivatives: For pyridinium compounds, which are preferred as CA IX inhibitors for their membrane-impermeance,

> the best substitution pattern at the pyridinium ring includes either only compact alkyls . . . , or 2, 6-dialkyl-4-phenyl-pyridinium moieties. . . . [T]he number of the substituents at the pyridinium ring seems to be less important for the activity of this series of CAIs. . . . The nature of these groups on the other hand . . . is the most important parameter influencing CA inhibitory properties (together with the linker between the benzenesulfonamide moiety and the substituted pyridinium ring). . . .

[Specification, at page 50, lines 14-22.] As still another example, the larger active site present in CA IX explains why "the 2, 4, 6-triphenyl-pyridinium- and 2, 6-diphenyl-pyridinium derivatives of homosulfanilamide and 4-aminoethylbenzenesulfonamide efficiently inhibit isozyme IX, although they act as very weak inhibitors for isozymes I, II and IV (Table 2)." [Specification, at page 49, line 32 to page 50, line 3.]

C. Labels or Visualizing Means

Conventional art teaches appropriate labels or visualizing means. Further, as taught in the instant Specification, a preferred label for the claimed imaging methods is fluorescein isothiocyanate (FITC):

> Further, labeled exemplary CA IX-specific inhibitors, such as labeled sulfonamides, for example, conjugated to fluorescein isothiocyanate (FITC), are shown to bind to the surface of MN/CA IX transfected cells, and not to control cells, only in hypoxia but not in normoxia. Those experiments confirm that CA IX-specific inhibitors, such as the sulfonamide compounds described herein, can specifically target MN/CA IX under conditions characteristic of intratumoral microenvironments.

[Specification, page 27, lines 1-6.] As indicated in Applicants' previous response (dated November 7, 2007) at page 17, "those experiments" are referring to the in vitro experiments of Svastova et al. (2004) which support the instant claims directed to in vivo imaging [Claims 69, 83-85 and 89-90.]. In view of the disclosure in the Specification that the active site of CA IX is larger than that of other CAs tested, one of skill in the art would expect that a MN/CA IX-specific inhibitor conjugated to a "label," "visualizing means" or "imaging" agent would be more selective for CA IX than the unconjugated inhibitor and more selective towards CA IX than other CA isozymes.

As pointed out in detail in the previous response dated November 7, 2007 (at pages 16-21), the guidance of the Specification for the selection of CA IX-specific inhibitors, from among the possible heterocyclic and aromatic compounds, has been more recently verified by new compounds that have been prepared and tested against MN/CA IX, as described in Svastova et al., FEBS Lett., 577(3): 439-445 (2004), Cecchi et al., J Med Chem., 48: 4834-4841 (2005), and Alterio et al., J Am Chem Soc., 128(25): 8329-8335 (2006). As evidenced by Cecchi et al., several of the sulfonamide CA IX inhibitors described in the instant specification have been conjugated with the fluorescent label FITC, and (as expected according to the teachings of the instant specification) the resulting bulkier, fluorescently-labeled compounds show improved affinity for CA IX, and improved specificity for CA IX over other critical CAs tested.

Also, as Applicants argued at pages 19-20 of the previous response, **clinical imaging trials have begun with the FITC-labeled conjugate of Compound 6** [reported in Alterio et al., 2006; identified as "Compound **1**"].

In summary, the instant Specification for the first time provides a structure-function analysis of the CA IX active site, and structure-function analysis of CA IX

inhibitors, which can be used in the design of additional CA IX-preferential aromatic and heterocyclic inhibitors. Applicants have provided exemplary and preferred CA IX-preferential inhibitors, each inhibitor having a complete structure indicated by formula or diagram, and have further provided a detailed structure/function analysis of 1) effects of heterocyclic versus aromatic rings in general; 2) effects of size and charge of the heterocyclic/aromatic ring; 3) effects of size, charge, and polarity of side-groups; and 4) effects of specific moieties of the exemplary inhibitors relative to their preference for CA IX. With such information, a would-be infringer could easily select a base aromatic or heterocyclic compound that favors CA IX [e.g., orthanilamide, 1,3-benzene-disulfonamide, homosulfanilamide and 4-aminoethyl-benzenesulfonamide], and simply substitute or add side-groups/moieties that favor CA IX in order to design a compound likely to inhibit CA IX preferentially.

Applicants respectfully submit that claims of an application are to be read in view of the specification [Musher Foundation, Inc. v. Albu Trading Co., 66 USPQ 183 at 186 (2d Cir. 1945); and Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 at 95 (Fed. Cir. 1986). Moreover, the "heterocylic and aromatic compounds" that are candidate CA IX inhibitors are subjected to screening assays, and shown to be potent and specific against CA IX, and/or membrane-impermeant. Once one of skill in the art has the guidance of the Specification, he or she would be easily guided as to which compounds would be more likely to favour CA IX. Further, virtual screening of databases for compounds with similar attributes to those shown to work well in the Specification allow one of skill in the art to find comparable candidate compounds that would also be expected to work in light of the Specification's disclosure.

Inapplicability of Case Law Cited

At the middle of page 4 of the Office Action, the Examiner asserts that because the specification provides no working examples for an in vivo method of imaging and diagnosis, the instant methods lack adequate written description, as in the Eli Lilly case:

> [T]he claimed invention is drawn to a method of imaging or diagnosing cancer using a compound identified by the screening method within the claim. However, no structural

> or specific functional characteristics of such an inhibitor is provided, nor is there any indication that the artisan actually implemented the method of [sic] so as to identify any inhibitor This situation is analogous to that of *Regents of the University of California v Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Because one skilled in the art would conclude that the inventors were not in possession of the claimed invention.

Applicants respectfully disagree, arguing as in their response dated June 27, 2007 at pages 18-20 that in distinction from the Eli Lilly case, and as set forth by the Federal Circuit in Enzo Biochem Inc. V. Gen-Probe Inc., [296 F.3d 1361 (Fed.Cir. 2002)] the instantly claimed invention does set forth "common features possessed by members of the genus," which "common features" are detailed above. The Eli Lilly case is clearly distinguishable from the instant application in that the involved U.C. patent claims, **as compositions of matter**, recombinant plasmids with cDNA encoding for (1) rat insulin, (2) human insulin, and (3) vertebrate and mammalian insulin. However, the UC inventors had only discovered the sequence for proinsulin (PI) and preproinsulin (PPI) **rat** insulin. The "genetic material" found to lack written description in Eli Lilly was the human insulin gene for which the native DNA sequence was **not** provided and could **not** be determined from the rat insulin DNA sequence. In the instant case, contrary to the Examiner's position that "no structural or specific functional characteristics of such an inhibitor is provided . . . ," Applicants have provided exemplary and preferred CA IX-preferential inhibitors (supra), each inhibitor having a complete structure indicated by formula or diagram, and have further provided a detailed structure/function analysis of CA IX preferential inhibitors.

Applicants respectfully further distinguish the Eli Lilly case from that of the instant application, in that the Applicants are not claiming as compositions of matter, that is, as compounds per se, the organic heterocyclic and aromatic compounds (Claims 67, 68 and 69), particularly heterocyclic and aromatic sulfonamides (Claims 87-90), more particularly cell membrane-impermeant heterocyclic and aromatic compounds (Claims 70 and 77-82), including cell membrane-impermeant aromatic or heterocyclic sulfonamides (Claims 72-75 and 83-86), further including positively-charged, cell membrane-impermeant aromatic and heterocyclic sulfonamides (Claim 84), and further

including cell membrane-impermeant pyridinium derivatives of aromatic and heterocyclic sulfonamides (Claims 73 and 85). Applicants are instead claiming the use of said compounds in the claimed methods. Said organic heterocyclic and aromatic compounds, that are useful in the claimed methods, are those that share certain **specific functionalities**, that is, for example, as indicated above with specific sulfonamide derivatives that inhibit CA IX's enzymatic activity in a screening assay with an inhibition constant K_1 less than about 50 nanomolar, and that are more potent inhibitors of MN/CA IX's enzymatic activity than that of each of CA I's, CA II's and CA IV's (Claims 67-69).

One of skill in the art would read the claims in the light of the Specification for the selection of candidate "heterocyclic and aromatic compounds" as CA IX-specific inhibitors, using the structure-function analysis provided at the least at page 47, line 28 to page 54, line 22 (supra). As stated in the MPEP § 2163 (I),

> Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. . . .

Applicants respectfully submit that they have described "distinguishing identifying characteristics" sufficient to show that they were in possession of the claimed invention.

Written Description Conclusion

The instant Specification provides not only characterization of the CA IX's active site, but also structure-function analysis of several heterocyclic and aromatic compounds that teach one of skill in the art how to choose heterocyclic and aromatic compounds that would be likely to preferentially inhibit CA IX's enzymatic activity. New compounds, designed using the guidelines of the instant Specification, confirm its teachings regarding preferred structures for CA IX-preferential inhibitors. Also, the diagnostic/prognostic methods comprise the use of compounds that are subjected to screening assays for potency and specificity against CA IX, and/or membrane impermeance. Applicants respectfully conclude that the Specification provides proper

disclosure to one of skill in the art, and a factual basis for the prediction that a wide range of organic heterocyclic and aromatic compounds, including those not specifically disclosed in the instant Specification, could have utility as CA IX-selective inhibitors. In addition, once CA IX-preferential inhibitor compounds have been identified, additional CA IX-preferential inhibitor compounds can be identified based on structural similarities, e.g., using **virtual screening**, as evidenced by Grüneberg et al., 2002 and Taylor et al., 2008 (copies enclosed).

Applicants respectfully conclude that the Specification meets the written description requirement of 112, 1st paragraph, for Claims 67-70, 72-75 and 77-90, and in accordance with the PTO's Written Description Guidelines, satisfies the written description requirement for a claimed genus, not only

> through sufficient description of a representative number of species by actual reduction to practice . . . [but also] by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. . . .

[Fed. Reg., Vol. 66, No. 4 (Jan. 5, 2001), at page 1106 (col. 3).]

> Applicants respectfully remind the Examiners that
>
> [t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. . . .
>
> . . . .
>
> Consequently, rejection of an original claim for lack of written description should be rare.

[MPEP § 2163(I)-(II); emphasis added.] Also, the PTO's Written Description Guidelines [Fed. Reg., Vol. 66, No. 4 (Jan. 5, 2001)] state:

> The Guidelines emphasize that the burden of proof is on the **examiner to establish that a description as filed is not adequate and require the examiner to introduce sufficient evidence or technical reasoning to shift the**

burden of going forward with contrary evidence to the applicant.

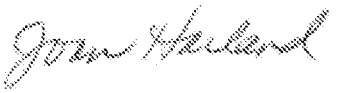
[*Id.* at page 1100, col. 3; emphasis added.] Applicants respectfully conclude that the Examiner has not introduced sufficient evidence to shift the initial burden of proof to the Applicants, but if hypothetically that burden had been shifted, the Applicants would have overturned that burden for all the reasons and evidence provided above.

Applicants respectfully submit that the claims meet the written description requirement for the claimed methods, comprising the use of a genus of organic heterocyclic and aromatic CA IX-specific inhibitors, and respectfully request that the Examiner reconsider andwithdraw the instant 35 USC 112, first paragraph rejection.

CONCLUSION

Applicants respectfully conclude that the claims are in condition for allowance, and earnestly request that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Agent for Applicants at (415) 981-2034.

Respectfully submitted,



Joan Harland, Ph.D.
Agent for Applicants
Registration No. 51,779

Dated: April 2, 2008